REMARKS

Entry of the foregoing, reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks which follow.

As noted in the Office Action Summary, claims 50-129 are pending. Claims 69 and 77 are canceled herein without prejudice or disclaimer. Applicants reserve the right to file at least one continuation application directed to any subject matter canceled herein.

Claims 68, 76, 82, 90, 93, 98, 101, 106, 109, 114, 117, 122, and 125 are amended herein. Basis for these amendments may be found throughout the specification as-filed, especially at page 21, line 9, page 24, lines 10 and 11, as well as in the claims as-filed. Thus, no prohibited new matter is presented herein.

Oath/Declaration

A substitute Declaration identifying the citizenship of each inventor and addressing the failure of inventor Mika Lahtinen to execute the Declaration was filed by Applicants on November 25, 2005.

Rejections Under 35 U.S.C. §112, second paragraph

Claims 66-81 stand rejected under 35 U.S.C. §112, second paragraph, as purportedly indefinite.

Claim 66 is rejected, as it is purportedly unclear as to whether the phrase "composition comprising an extracellular superoxide dismutase" is a protein or a nucleic acid molecule encoding an extracellular superoxide dismutase protein. Likewise, claims 68-70, and claims 76-78, as dependent upon claim 66, are rejected to, as there is purportedly insufficient antecedent basis for the phrase "the nucleic acid" in the claims. Dependent claim 74 is rejected, because it is purportedly unclear if the phrase "composition comprising an extracellular superoxide dismutase" refers to a protein or a nucleic acid molecule encoding an extracellular superoxide dismutase protein. Claim 66 is rejected for the recitation of the phrase "composition comprising an extracellular superoxide dismutase", as it is purportedly unclear whether if it refers to a nucleic acid or a protein.

In response, to clarify the claimed subject matter, the claims are amended to recite "protein" wherever appropriate, and the claims are amended to provide proper antecedent basis.

In light of the above, Applicants request that these rejections be withdrawn.

Rejections Under 35 U.S.C. §112, first paragraph

Claims 50-129 stand rejected under 35 U.S.C. §112, first paragraph, for purportedly lacking sufficient enablement. The Office asserts that the art of gene therapy is highly unpredictable, and that the specification is only enabling for administering a composition comprising a nucleic acid vector comprising extracellular superoxide dismutase, wherein the vector is an adenoviral vector.

In the interest of furthering prosecution, the claims, as relating to vectors, are amended herein to recite retroviruses, adeno-associated viruses, lenti viruses, and adenoviruses. Further, recitation of Sendai viruses has been removed.

Applicants submit that the claims, as amended herein, are enabled. In support, Applicants note that adeno-associated virus (AAV) vectors have a similar structure as an adenovirus. The cloning vector contains CMV promoter followed by cDNA and a poly-A tail. Because these are the basic elements needed for mRNA synthesis, and EC-SOD does not require any extra elements for its expression, an AAV virus system can express EC-SOD in its functional form. Furthermore, AAV can, and has been shown, to successfully infect vascular wall cells (see, for example, Nitta Y et al., *J Gene Med.* 2005, Oct; 7(10):1348-55).

MLV (murine leukemia retrovirus) retroviruses have also been shown to have the ability to infect a vascular wall (see Yla-Herttuala et al. *J Clin Invest.* 1995 Jun;95(6):2692-8). Lentiviruses, like HIV, are also potential gene therapy vectors because they are able to transduce cells that cycle less frequently. These viruses have been shown to express various different kinds of cDNAs. Recently there have been reports showing the correlation between carcinogenesis and retrovirus integration. These reports have mainly focused on hematopoietic cells or cells that otherwise are cycling frequently. It can be suggested, based on these studies, that retroviruses integration (site directed mutagenesis) does not cause carcinogenesis by itself. Because the proliferation of vascular wall cells is limited, it is highly unlikely

that retro/lentivirus integration to vascular smooth muscle cell genome would cause transformation of cells to carcinogenic cells. Consequently, all of the above mentioned vectors are enabled, and undue experimentation would not be required to use them.

Applicants further note that the claims reciting a "nucleic acid encoding a translation or transcription product that leads to the production of extracellular superoxide dismutase protein" (*i.e.*, claims 82, 90, 98, 106, 114 and 122) are amended herein to recite a "nucleic acid encoding a translation and/or a transcription product of an extracellular superoxide dismutase protein."

The Office also comments on the claims, as reading on "the administration of a composition comprising cell containing a nucleic acid encoding EC-SOD". In response Applicants submit that the amended claims do not read on a cell.

Claims 89-129 are rejected under 35 U.S.C. §112, first paragraph, as purportedly failing to comply with the written description requirement. The Office refers to the term "nucleic acid encoding a translation or a transcription product that leads to the production of extracellular superoxide dismutase", as not being sufficiently supported by the description. As the claims are amended to no longer recite this phrase, Applicants submit this rejection is moot.

In light of the above, Applicants request that the rejections under 35 U.S.C. §112, first paragraph, be withdrawn.

Rejections Under 35 U.S.C. § 102

Claims 68, 67, 72-75, 80, 81, 98, 99, 104-107, 112-115, 120-123, 128 and 129 are rejected under 35 U.S.C. §102(b), as purportedly anticipated by Marklund et al. (U.S. .Patent No. 5,366,729) as evidenced by French et al. (U.S. Patent No. 6,290,949). Applicants traverse.

Applicants submit that Marklund fails to recite every element of the presently claimed invention, as amended herein. To anticipate a claim, a single prior art reference must teach each and every element of the claimed invention. *See* M.P.E.P. § 2131; *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986).

Marklund discloses EC-SOD variants having the superoxide dismutating property of the native EC-SOD, and a modified binding to heparin, as well as compositions comprising such variants. The Office asserts that Marklund discloses individuals that have a myocardial infarction, and that French shows that restenosis can occur incident to myocardial infarction.

Applicants note that Marklund does not provide their own evidence. Instead, Marklund merely refers to prior art, stating that SOD (not EC-SOD) exhibits these characteristics. In contrast to the SOD disclosed by Marklund, the extraordinary protective role of EC-SOD is believed to be due to its natural extracellular expression and the fact that it is glycosylated, with the protein having a substantially longer half-life than any other proteins of the family of SOD proteins. Furthermore, EC-SOD, in contrast to SOD1 or SOD2, displays a striking ability to bind to cell membrane heparin sulphate proteogylcans, where it removes superoxide anions that would otherwise damage the cell surface. Thus, the enzymes are not interchangeable in nature, nor would an expert be lead to substitute one for the other with a mitochondrial or cytoplasmic protein with an extracellular protein in an experimental set-up. In fact, they have previously been shown to exert different effects, *e.g.* SOD1 alone plays a significant role in ALS, whereas SOD2 alone is critical for cell survival and EC-SOD alone has been shown to be beneficial in connection with myocardial infarcts. Furthermore, the differences between SOD and EC-SOD regarding *e.g.,* distribution are also stated in a patent publication by French et al. (see, for example, U.S. Publication No. 2002/0061299), cited by the Examiner. Thus, SOD is not interchangeable with EC-SOD.

The Office cites French et al. as disclosing that restenosis can occur incident to myocardial infarction. In response, Applicants note that myocardial infarction is a condition in which blood circulation is suddenly stopped causing lack of oxygen in the tissue down stream of ischemia site. Often this injury is connected to ischemia-reperfusion damage in which after thrombosis oxygen rich blood is circulating through the injury site. The ischemia is causing oxygen free radical formation in the tissue of injury site and subsequent cellular changes *e.g.*, increasing permeability of tissue. When oxygen rich blood is circulating again through the injury site, it is increasing the injury.

Restenosis is a vascular wall response to balloon angioplasty of stenting in which angioblasty treatment causes short-term vascular trauma to vascular wall and surrounding tissue. One of the consequences of angioblasty is that it increases the oxygen free radical formation. A more important consequence is that it removes endothelial layer at the angioblasty site. Restenosis is the attempt of vascular wall to heal the damage by forming neointima that mostly contains smooth muscle cells and later is covered by forming neointima that mostly contains smooth muscle cells and later is covered by endothelial cell layer. Therefore, restenosis and myocardial infarction are two separate medical conditions, wherein the earlier one is caused by atherosclerosis and the later one caused by medical treatment.

Additionally, Marklund does not disclose testing EC-SOD in any disease model, but only administered recombinant EC-SOD protein variants to rabbits, evaluating the heparin affinity.

Thus, Applicants submit that Marklund, supported by French, does not recite each and every element of the invention as claimed herein.

Claims 50-53, 57-61, 65-69, 73-77, 81-85, 89-92, 97-101, 105-108, 113-117, 121-125 and 129 stand rejected under 35 U.S.C. §102(e) as purportedly anticipated by French et al. (U.S. Publication No. 2002/0061299) as evidenced by French et al. (U.S. Patent No. 5,366,729).

As noted, U.S. Publication No. 2002/0061299 (French) relates to a method for using anti-oxidant gene therapy to protect the intact mammalian heart against myocardial infarction, wherein EC-SOD is chosen as the antioxidant enzyme to be produced. Restenosis is not disclosed. Restenosis and myocardial infarction are two separate medical conditions, which is further explained in the above. Therefore, French does not recite each element of the present invention.

Applicants request that the rejections under 35 U.S.C. § 102 be withdrawn.

Rejections Under 35 U.S.C. § 103

Claims 50-129 stand rejected under 35 U.S.C. §103(a) as purportedly unpatentable over French et al. (U.S. Patent No. 6,290,949) in view of French (U.S. Publication No. 2002/0061299). Applicants traverse.

In order to establish a case of *prima facie* obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation to modify the reference or combine reference teachings, (2) there must be a reasonable expectation of success, and (3) the prior art reference(s) must teach or suggest all of the claim limitations. *See* M.P.E.P. 2142. Applicants respectfully submit that these criteria have not been met in the present Office Action. The cited references, alone or in combination, fail to recite all of the elements of the presently claimed invention or to provide an expectation of success or motivation to arrive at the claimed invention.

French et al. (U.S. Patent No. 6,290,949) disclose the administration of a composition to a mammal, comprising a nucleic acid encoding superoxide dismutase for the treatment of restenosis. French does not disclose EC-SOD, as noted by the Office. However, the Office asserts that in view of French et al. (U.S. Publication No. 2002/0061299), it would be obvious to exchange SOD for EC-SOD in French et al. (U.S. Patent No. 6,290,949). Applicants respectfully disagree.

No experimental data for any of these therapeutic genes mentioned in U.S. Patent No. 6,290,949 is provided, including for SOD. The only data provided in the cited references is that of the vector and its efficiency in being introduced into cells, as detected and determined by the expression of a reporter construct in said cells. Therefore, it is not disclosed or suggested that any therapeutic gene mentioned, could be introduced, and thereafter exert an effect on the disease as claimed. As previously stated, Applicants submit that it would not be obvious to SOD with EC-SOD, as these are different enzymes that are known in the art to generate different effects.

Thus, the cited references, in combination, fail to disclose each element of the present invention and to provide any expectation of success. Applicants request that the rejections under 35 U.S.C. § 103 be withdrawn.

CONCLUSION

It is respectfully submitted that all rejections have been overcome by the above amendments. Thus, Notice of Allowance is respectfully requested.

In the event that there are any questions relating to this Amendment or the application in general, it would be appreciated if the Examiner would contact the undersigned attorney by telephone at (703) 836-6620 so that prosecution of the application may be expedited.

Respectfully submitted,

BUCHANAN INGERSOLL PC
(INCLUDING THE ATTORNEYS FROM BURNS DOANE SWECKER & MATHIS)

Date: December 27, 2005

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Enclosures: Abstract of the Disclosure